Remarks

Claims 1-4, 6-25, 27-35 and 49-52 currently are pending in the present case. Claims 6-7 were withdrawn from consideration as directed to a non-elected species. Applicants are canceling claims 6-9, 17-22, 27-31, 35, and 49-52 herein, rendering any rejections with respect to these claims moot. Claims 1-4, 10-16, 23-25 and 32-34 are amended and new claims 53-54 are added. Applicants reserve the right to prosecute the canceled subject matter in a later-filed divisional or continuation application. Claims 1-4, 8-25, 26-35, and 49-52 have been examined.

Claims 1-4, 8-12, 17-23, 27-29 and 35 stand rejected as obvious over the combination of Z'hu et al. and Chao et al. Z'hu et al. are cited for teaching a nucleic acid encoding a recombinant single-chain human MHC class II molecule comprising an antigenic peptide bond via a linker to the extracellular domain of the MHC class II beta chain. The Office concedes that Z'hu et al. does not teach glutamic acid decarboxylase (GAD) peptides in association with MHC class II molecules, but cites Chao et al. for teaching GAD 65 peptides that bind to a murine MHC class II haplotype associated with diabetogenesis in NOD mice, including the instant SEQ ID NOS: 1 and 2. The Office Action relies on guidance in Z'hu et al. to provide the motivation to use the GAD peptides of SEQ ID NOS: 1 and 2 with its engineered HLA molecules.

To make out a prima facie case of obviousness against a claim, the Office is required to make a showing as to all three of the following: (1) the cited references must teach or suggest all elements of the rejected claim; (2) the references or the prior art must provide motivation to combine or modify the teachings of the cited art to achieve the claimed invention; and

(3) there must be a reasonable expectation of success for the combined art. M.P.E.P. §2143. Failure to meet only one of these standards is fatal to a showing of prime facie obviousness.

Applicants first submit that the prior art cited here do not teach or suggest all of the elements of the present claims in their amended form. Applicants have amended claims 1 and 23 to recite a stable glutamic acid decarboxylase (GAD)-peptide-specific Class II *MHC* complex which comprises (1) the extracellular portion of the β chain of a Class II *MHC* molecule ... and (2) a GAD peptide that binds to said Class II molecule. Amendments to the dependent claims were necessitated by the amendments to the independent claims. New claims 53-54 also have been added. These claims are directed to tetrameric complexes. Support for these claim amendments can be found throughout the specification and, for example, at paragraphs 7, 56, 67 and Examples 1 and 11. Support for complexes that are tetramers may be found throughout the specification and, for example, at paragraphs 11, 54, 73 and Examples 4 and 7-12.

The claimed complex is not taught or suggested in Z'hu et al. or Chao et al. Applicants refer the Office to previous responses for a description of what Z'hu et al. teach. The Office concedes that Z'hu et al. fail to teach all of the elements of the claimed invention. Z'hu et al. do not teach or even suggest autoantigen peptides of any type and do not mention or suggest GAD peptides generally or any specific GAD peptides. Zhu et al. do not teach or suggest autoimmune disease-associated Class II *MHC* molecules generally or any particular such molecules, for example, I-Ag7 or DQ.

The Office relies on the teachings of Chao et al. to make up for the deficiencies of Z'hu et al. However, while Chao et al.

discloses GAD 65 peptides and MHC II alleles individually, they do not teach or suggest that GAD 65 peptides can bind to I-Ag7 or DQ to form a stable complex as required by the amended claims and they do not teach or suggest the GAD peptides which should be used for this purpose. Accordingly, the combination of Z'hu et al. and Chao et al. do not teach or suggest all of the elements of the claimed invention.

Applicants also submit that there is no motivation or suggestion to modify and combine the teachings of the cited references to create the claimed stable GAD-peptide-specific I-Ag7 or DQ complex. Absent impermissible hindsight, relying on the findings described in the present specification, there is no motivation for the skilled person aware of the art, to combine the teachings of Chao et al. with the teachings of Z'hu et al. First of all, Chao et al. identify epitopes of GAD65 that bind to I-Ag7 *in vivo*, but do not mention or even hint at the stable complexes of the present invention. In discovering the immunogenic epitopes, moreover, Chao et al. recognized that the "degree of affinity does not correspond to the degree of immunogenicity." Chao et al., page 33, second full paragraph. Thus, Chao et al. question the degree of affinity of the peptides they identified.

The skilled person would have been aware of the difficulties in preparing autoantigen-specific complexes of the type claimed here, for example, Carasco-Marin et al., *J. Immunol.* 156:450-458, 1996 and Carasco-Marin et al., *Res. Immunol.* 148(5):291-301, 1997, which are submitted in the accompanying Information Disclosure Statement. These references bear dates near the dates of Z'hu et al. and Chao et al.

First, Carasco-Marin et al., (1996) states, *inter alia*, that I-Ag7 molecules bind peptides poorly, have short half lives and have a very low propensity to form stable complexes with peptides (See, *inter alia*, page 450, second full paragraph and page 452, third and fourth full paragraphs). Furthermore, the discussion throughout the reference, for example, at page 456, left-hand column, emphasizes repeatedly that I-Ag7 molecules interact poorly with self peptides. Indeed, the study found no peptides that formed a long-lived or SDS-stable complex with I-Ag7, including GAD 524-543, a peptide identified by Chao et al. See Carasco-Marin et al. (1996), Table IV. These same authors found that both I-Ag7 and DQ have decreased SDS stability. See Carasco-Marin et al., (1997), page 294, fourth full paragraph and Table II. These findings clearly support the skepticism of Chao et al., and other skilled artisans at that time, that MHC class II molecules could bind peptides such as GAD peptides to form a stable molecular complex. Applicants submit that the art as a whole strongly teaches against any expectation of success for the stable complexes that are claimed here. Accordingly, the cited references, in light of the art as a whole, do not provide motivation to combine their teachings with any reasonable expectation of success in achieving the stable molecular complex of the claimed invention.

Applicants would again like to direct the attention of the Office to the previously submitted declaration under 37 C.F.R. § 1.132 by Dr. Liu, an inventor of this application. Applicants submit that the Liu Declaration supports the patentability of the present amended claims. In particular, Dr. Liu provides further evidence that no reasonable expectation of success was found in the art at the time this application was filed. The Examiner

claims that the declaration is directed to tetramers, and as such, is not directed to the claimed invention. The declaration refers to stable Class II MHC multimeric complexes, often referred to as "tetramers" in the art. These terms would be understood by skilled persons and are used in the present specification.

Accordingly, Dr. Liu's declaration is pertinent to the examination of the amended claims. This declaration shows that while MHC class II molecules and GAD peptides may have been known individually; there was no reasonable expectation of success for stable I-Ag7- or DQ-peptide complexes because the art taught that making and using such MHC class II complexes was unpredictable and risky. Accordingly, Applicants request that the Examiner reconsider the Declaration and the evidence it provides, in view of the above arguments and amendments.

In summary, Applicants respectfully submit that the cited references, alone or in combination, do not teach or suggest the claimed complexes and that there is no motivation to modify those references with a reasonable expectation that stable GAD peptide-binding I-Ag7 or DQ complexes as claimed would be successful. Z'hu et al. do not teach or suggest that GAD peptides would work with their methods. Chao et al. and the art generally express doubt and skepticism regarding stable complexes such as the claims require. Therefore, the Office cannot meet all three of the criteria necessary for making out a prima facie case of obviousness.

For the above reasons, Applicants respectfully submit that the Office cannot make out a case of prima facie obviousness against the claims as amended. In view of the evidence in the art indicating that stable binding of peptides to MHC class II

molecules was unpredictable and risky or even not possible to achieve, the Examiner's case of obviousness could only be the product of impermissible hindsight based on the surprising teachings and findings of the present invention. Applicants therefore request that this rejection be withdrawn.

Claims 1-5, 8-13, 15, 17-24, 26-30, 26-30, 32-35 and 49-52 are rejected as obvious over Z'hu et al. in view of both Chao et al. and Crawford et al. The Office relies on the teachings of Crawford et al. with respect to biotinylation of MHC class II/ peptide complexes in combination with the disclosures of Z'hu et al. and Chao et al.

The deficiencies in the combined disclosures of Z'hu et al. and Chao et al. are discussed at length above. Applicants refer the Office to these remarks and reassert that the combination of Z'hu et al. and Chao et al., do not render the amended claims obvious.

Crawford et al. do not teach or suggest the invention claimed here and do not make up for the deficiencies of the earlier-cited references. Crawford et al. do not provide any motivation to combine the Z'hu et al. and Chao et al. references or provide any reasonable expectation of success for such a combination if the skilled person were to happen upon it. Crawford et al. only suggest covalent attachment of peptides to the MHC molecule and using a biotinylated tag, but do not assist the Office in making out a prima facie case of obviousness against the claims here rejected. Applicants therefore request that this rejection be withdrawn because the Office cannot meet all of the necessary criteria for making out a prima facie case of obviousness based on this combination of references.

Claims 1-5, 8-12, 14, 16-23, 25-29, 31, 35 and 49-52 are rejected as obvious over Z'hu et al. in view of Chao et al. and Rhode et al. Rhode et al. are cited for teaching oligohistidine tags.

The deficiencies of the Z'hu et al. and Chao et al. references are discussed above. In summary, these references provide no motivation to combine their disparate teachings because the references, especially in light of the art, teach doubt that the inventive compounds can be achieved. Neither the cited references nor the art in general provide any reasonable expectation of success should the combination be attempted. Applicants refer the Office to the discussion above, the art provided with the accompanying Information Disclosure Statement and the Liu Declaration, which provide evidence that the art provided no expectation of success for the present invention.

The Rhode et al. reference does not make up for the deficiencies of Z'hu et al. and Chao et al. This reference is cited for its teachings related to oligohistidine tags. Nothing in this reference provides a motivation to combine the teachings of Z'hu et al. and Chao et al. to achieve the invention claimed here or provides any reasonable expectation that such an combination would be successful merely because of the additional presence of a histidine tag. Applicants respectfully submit that the Office cannot make out a prima facie case of obviousness against the claims pending here and request that this rejection be withdrawn.

Finally, new claims 49-52 are rejected under 35 U.S.C. 112, first paragraph, as containing new matter. The Office asserts that the claim phrase "auto-immune disease-associated Class II MHC molecule" is new matter and not supported by the

specification as filed. Applicants traverse this rejection and refer the Office to paragraph 67, which discusses I-Ag7 and DQ as an MHC molecule "associated with a disease state." This same paragraph discusses the antigenic peptides associated with I-Ag7 and DQ as suspected in the etiology of autoimmune disease. In particular, the Office's statement that only I-Ag7 is supported as an autoimmune disease-associated Class II molecule is erroneous. The specification discusses these molecules generally and provides I-Ag7 and DQ as examples. Applicants submit that word-for-word support is not required by the statute and that the claims are fully supported for this language. However, to facilitate prosecution, Applicants have canceled claims 49-52 and request withdrawal of the rejection. The claims are now amended to recite complexes comprising I-Ag7 and DQ.

Applicants request favorable consideration of the amended claims at this time.

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